# A Pooled Analysis of Diagnostic Value of $^{99m}$Tc-Ubiquicidin (UBI) Scintigraphy in Detection of an Infectious Process

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**Purpose:** Although the data are promising from limited studies with technetium-99m ubiquicidin ($^{99m}$Tc-UBI) scintigraphy in detection of infection in humans, these studies have had a limited sample size. This study was conducted to provide a systematic review and meta-analysis of the reported diagnostic accuracy of $^{99m}$Tc-UBI scintigraphy in detection of an infectious process.

**Materials and Methods:** The PubMed/MEDLINE, Web of Science, EMBASE, and Google Scholar literature databases were systematically searched to find the relevant human studies on $^{99m}$Tc-UBI scintigraphy. For each eligible study, the true-positive, false-positive, true-negative, and false-negative findings at $^{99m}$Tc-UBI scintigraphy were recorded, and the overall statistical parameters were acquired.

**Result:** Ten studies carried out from 2004 to 2010 were included in the analysis. The pooled data sensitivity was 94.5 % and with a 95% confidence interval of 91.2%–96.8%. The pooled specificity was still as high as about 92.7%. The range of reported specificity was from 80% to 100%. The overall accuracy was 93.7% (95% CI: 91.2%–95.7%).

**Conclusion:** The study demonstrated that $^{99m}$Tc-UBI scintigraphy can be used to identify an infectious process with admirable accuracy in early views; however, further investigations are recommended.

**Key Words:** $^{99m}$Tc-UBI scan, antimicrobial peptides, infection

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The prompt and timely clinical diagnosis of infection can be challenging, but it is associated in a crucial way with a patient's care management. Current available radiopharmaceuticals are often unable to differentiate between sterile inflammation and infection. Several pharmaceuticals labeled with various radioisotopes, such as liposomes labeled with technetium-99m ($^{99m}$Tc),[1] immunoglobulins,[2,3] the avidin-biotin system,[4] antigranulocyte antibodies and antibody fragments, chemotactic peptides, cytokines, interleukins, platelet factor-4, and ciprofloxacin labeled with $^{99m}$Tc,[5] have been applied, but an optimal radiotracer has not yet been established. Therefore, autologous leukocytes labeled with $^{111}$In or $^{99m}$Tc-HMPAO are still considered the gold standard despite their limitations.[6] Consequently, the practice of directly targeting infectious agents with radiolabeled antibiotics or antimicrobial peptides was introduced,[7] and a number of radiolabeled peptides have been assessed.[8,9] Among the several radiolabeled peptides options, $^{99m}$Tc-labeled cationic antimicrobial peptides originating from ubiquicidin (UBI) are increasingly used in the diagnostic evaluation of patients.[10,11]

Although results from limited preclinical and pilot studies in patients are promising,[12,13] they had a limited sample size. So we have performed a meta-analysis of diagnostic studies regarding the accuracy of $^{99m}$Tc-UBI 29–41 scintigraphy in the identification of infection.

## MATERIALS AND METHODS

### Identification and Eligibility of Pertinent Investigations

An attempt was made to identify all investigations regarding the diagnostic accuracy of ubiquicidin (UBI) labeled with $^{99m}$Tc for the detection of infection in patients.

All pertinent investigations were included, not considering the type of UBI used and regardless of the location of disease. The PubMed/MEDLINE, Web of Science, EMBASE, and Google Scholar literature records were systematically searched for publications from January 1965 up to September 2012. The search strategy was based on the terms "99mTc-ubiquicidin scintigraphy," "99mTc-UBI scintigraphy," "antimicrobial peptides scan using UBI," "ubiquicidin scan," and "UBI scan." Experimental investigations on animals were excluded.

### Data Extraction

First, 2 researchers (A.O., M.A.) obtained data from eligible investigations separately and discussed discrepancies, and when agreement was not attained, a third researcher (M.A.) helped to resolve the difference. For each study, several items were recorded such as authors' names, publication year, number of eligible patients, inclusion and exclusion criteria, study design (prospective, retrospective, or unclear), demographic characteristics of patients, location of disease, type of synthetic fragments UBI (UBI 18–35 or UBI 29–41), methods used for the interpretation of the results (qualitative or semiquantitative), and the number of readers who interpreted the final diagnosis. The explanation of the reference method used to document infection was noted. The quality of evidence using the Critical Appraisal Skills Programme tool for diagnostic tests was also considered.[14]

### Statistical Analysis

For each study, the number of true-positive, false-positive, true-negative, and false-negative findings at $^{99m}$Tc-UBI scintigraphy, as compared with the standard method, was recorded in a $2 \times 2$ table. We calculated true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FP) values by summing up the individuals of each category from all studies included. Then sensitivity was calculated as TP/TP + FN and specificity as TN/TN + FP. The accuracy was also

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**TABLE 1.** Characteristics of Participants Included in the Studies

| Study | Study Design | Mean Age; Range, yr | Men/Women | Reported Disease(s) |
|---|---|---|---|---|
| Assadi et al,[15] 2011 | Prospective | 48.9; 20–69 | 12/8 | Suspicion of osteomyelitis, due to diabetic foot ulcers inflammation at the site of prosthesis, or bone fractures |
| Akhtar et al,[16] 2005 | Prospective | 31.7; 5–75 | 9/9 | Suspected bone, soft-tissue, or prosthesis infections |
| Aryana et al,[17] 2012 | Prospective | 47; 20–79 | 18/16 | Painful total hip prosthesis |
| Gandomkar et al,[12] 2008 | Prospective | 55; 35–75 | 5/2 | Suspected bone or soft-tissue infections, osteomyelitis, cellulitis |
| Arteaga de Murphy et al,[18] 2010 | Prospective | 45; 18–88 | 56/92 | FUO, osteomyelitis, diabetic foot, prosthesis infection, septic arthritis, bacteremia, suspected bone infection |
| Sepulveda-Mendez et al,[13] 2010 | Retrospective | NR | NR | FUO |
| Dillmann-Arroyo et al,[19] 2011 | Retrospective | 50; NR | 15/12 | Suspected vertebral osteomyelitis |
| Melendez-Alafort et al,[20] 2004 | Prospective | 11.2; 2–15 | 4/2 | Suspected bone infection |
| Fard-Esfahani et al,[21] 2010 | Prospective | 58; 48–79 | 10/5 | Suspicion of osteomyelitis due to diabetic foot |
| Vallejo et al,[22] 2008 | Prospective | 50; 27–65 | 8/5 | Suspected mediastinitis after cardiac surgery |

NR indicates not reported; FUO, fever of unknown origin.

calculated as TP + TN/TP + TN + FP + FN. The confidence intervals of proportions were calculated using the Exact Binomial Method. The data analysis was carried out using STATA software, version 11 (StataCorp, College Station, TX, USA).

## RESULTS

Ten studies carried out from 2004 to 2010 were included in the analysis. The characteristics of these studies are shown in Tables 1, 2, and 3.

Sensitivity: Six out of 10 studies reported a perfect sensitivity for the technique. The sensitivities for others were from 40% to 97.5%. The pooled data sensitivity was 94.5 % and with a 95% confidence interval of 91.2%–96.8%.

Specificity: Unlike sensitivity, the specificity is heterogeneous among the studies; however, the pooled specificity is still as high as about 92.7%. The range of reported specificity was from 80% to 100%, and only 2 studies reported a perfect specificity.

The values for all included studies and summary values have been summarized in Table 3.

## DISCUSSION

An infection process that includes bone, soft tissue, and orthopedic device infection is a critical problem that needs rapid diagnosis and treatment, especially with an incremental growth in resistance to new broad-spectrum antibiotic drugs.[5] The diagnosis of an infection process is often not clear-cut, and it is associated with the severity of bone or soft-tissue involvement as well as with the host's reaction to pathogenic agents.[23]

Nuclear medicine techniques play an important role in this field, and several radiopharmaceuticals have been applied in the past, such as immunoglobulins,[2,3] liposomes, ciprofloxacin labeled with $^{99m}$Tc,[1] the avidin-biotin system,[4] antigranulocyte antibodies and antibody fragments, chemotactic peptides, cytokines, interleukins, and platelet factor-4[5]; nevertheless, the optimal radiopharmaceutical has not yet been developed.

The optimal radiotracer should facilitate early diagnosis, should result in little absorbed radiation exposure, and should enable the differentiation of inflammation from infection.[24] Safety, cheapness, availability, and fast clearance from the blood and the body are further characteristics of an ideal radiopharmaceutical. Moreover, it should be simple and rapid in preparation.[24] Almost all present available radiopharmaceuticals possess some of these criteria, but up to now, no single radiotracer is known in clinical practice that can enable undoubted discrimination of infection from sterile inflammation.[24]

However, among all radiotracers, antimicrobial peptides that attach directly to bacteria are preferred, relative to other radiopharmaceuticals,[16] and among all the human-derived antimicrobial peptides tested, the UBI 29–41 has demonstrated the greatest promise.

$^{99m}$Tc-labeled UBI 29–41 is a small synthetic peptide (amino acid sequence TGRAKRRMQYNRR; 1693 Da), which originated

**TABLE 2.** Characteristics of $^{99m}$Tc-UBI Scintigraphy in Included Diagnostic Studies

| Study | $^{99m}$Tc (MBq) | Type of Synthetic Fragments UBI | Scanning Time, min | No. of Readers | Analysis | Blinding | Reference Standard |
|---|---|---|---|---|---|---|---|
| Assadi et al,[15] 2011 | 740 | 29–41 | 1–15, 30, 45, 60, 120, 240 | 2 | SQ, Q | Yes | C, FU, H, M, R |
| Akhtar et al,[16] 2005 | 370–400 | 29–41 | 1–10, 30, 60, 120, 240 | NR | SQ, Q | Yes | C, M, R |
| Aryana et al,[17] 2012 | 740 | 29–41 | 1–30 | 2 | SQ, Q | Yes | C, FU, H, M, R |
| Gandomkar et al,[12] 2008 | 555–740 | 29–41 | 1–45, 30, 60, 120 | NR | SQ, Q | Yes | C, FU, M, R |
| Arteaga de Murphy et al,[18] 2010 | 555–740 | 29–41 | 30, 120, 240, 1440 | 2–3 | SQ, Q | Yes | C, R |
| Sepulveda-Mendez et al,[13] 2010 | 370–740 | 29–41 | 120, 360 | 2 | Q | Yes | C, FU, M, R |
| Dillmann-Arroyo et al,[19] 2011 | NR | 29–41 | 120 | 2 | Q | Yes | C, FU, H, M, R |
| Melendez-Alafort et al,[20] 2004 | 74–222 | 29–41 | 1, 30, 120, 240, 1440 | 3 | SQ, Q | Yes | H, R |
| Fard-Esfahani et al,[21] 2010 | 555–740 | 29–41 | 1–10, 60, 120 | 3 | Q | Yes | C |
| Vallejo et al,[22] 2008 | 740 | 29–41 | 120 | 2 | SQ, Q | Yes | C, FU |

NR indicates not reported; SQ, semiquantitative; Q, qualitative; C, culture; FU, clinical follow-up; H, histologic; M, microbiologic or laboratory examination other than culture; R, radiologic examination, including radiography, CT, MR imaging, and scintigraphy.

**TABLE 3.** The Summary of Original Studies Included in the Analysis

| Study | Max T/NT Time, min | Max T/NT (Mean or Range) | Case | TP | TN | FP | FN | Se% (CI) | Sp% (CI) | Ac% (CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| Assadi et al,[15] 2011 | 15 | 1.54–2.94 | 20 | 17 | 3 | 0 | 0 | 100 | 100 | 100 |
| Akhtar et al,[16] 2005 | 30 | 2.75 | 18 | 14 | 3 | 1 | 0 | 100 | 80 | 94.4 |
| Aryana et al,[17] 2012 | 1–30 | 1.90 | 34 | 6 | 24 | 4 | 0 | 100 | 85.7 | 88.2 |
| Gandomkar et al,[12] 2008 | 30 | 2.10 | 7 | 5 | 2 | 0 | 0 | 100 | 100 | 100 |
| Arteaga de Murphy et al,[18] 2010 | 30 | 2.1–2.8 | 148 | 77 | 64 | 4 | 3 | 96.3 | 94.1 | 95.3 |
| Sepulveda-Mendez et al,[13] 2010 | — | — | 207 | 118 | 82 | 4 | 3 | 97.5 | 95.4 | 96.6 |
| Dillmann-Arroyo et al,[19] 2011 | — | — | 27 | 20 | 6 | 1 | 0 | 100 | 88 | 96.3 |
| Melendez-Alafort et al,[20] 2004 | 120 | 2.18 | 6 | 5 | 1 | 0 | 0 | 100 | 100 | 100 |
| Fard-Esfahani et al,[21] 2010 | — | — | 15 | 6 | — | — | 9 | 40 | — | — |
| Vallejo et al,[22] 2008 | — | — | 13 | 5 | 6 | 1 | 1 | 83.3 | 85.7 | 84.6 |
| Summary | | | 495 | 273 | 191 | 15 | 16 | 94.5 (91.2–96.8) | 92.7 (88.3–95.9) | 93.7 (91.2–95.7) |

TP indicates true positive; TN, true negative; FP, false positive; FN, false negative; Se, sensitivity; Sp, specificity; Ac, accuracy.

from human UBI and which attaches preferentially to bacteria in vitro and not to activated leukocytes.[25] The $^{99m}$Tc–UBI 29–41 scans have depicted the most promising results for delineation between infection and inflammation in animal models[11,26,27] and also in inadequate human investigations.[12,13,15,16,18,19,28,29]

Our meta-analysis showed that $^{99m}$Tc–UBI 29–41 scans had a reasonably high differentiation ability in recognizing an infection among patients who had possible infection in the soft tissue, musculoskeletal system, and prosthesis. The overall accuracy was 93.7%.

The $^{99m}$Tc–UBI 29–41 scan has been applied to the diagnosis of infection in limited clinical situations such as osteomyelitis and soft-tissue infections,[15,16] spondylitis,[19] fever of unknown origin,[13] prosthesis,[17] and endocarditis (which we used in limited cases); except for diabetic patients with a poor vascular bed,[21] high sensitivities and specificities were mentioned. Systematic assessment of diagnostic ability in these settings would be helpful to illustrate the most favorable spectrum of applications for this scintigraphic modality.

Consequently, $^{99m}$Tc UBI 29–41, without localization in sterile inflammation and with an absence of immunological side effects, may be considered an option for leukocyte labeling, which is still applied as the gold standard for detection of infection in nuclear medicine. It can also be used in leukopenic patients. Furthermore, it was demonstrated that $^{99m}$Tc–UBI (29–41) accumulation directly represents the number of viable bacteria, and it is applicable for the monitoring of antibiotic treatment.[28,30]

Furthermore, in all studies, the maximum contrast (A/N ratio) was obtained in the earliest time post–$^{99m}$Tc-UBI injection.[12,16] These results may indicate a first pass-like distribution with strong avidity of the radiotracer in the trend of its targets, resulting in the easy diagnosis of infection as early as few minutes postinjection. In addition, $^{99m}$Tc-UBI 29–41 scans illustrated rapid localization to the target region and fast renal clearance, with insignificant liver uptake and hepatobiliary excretion.[12,16,20]

In our meta-analysis, a number of reference standard methods were used in the studies, including cultures and other microbiologic examination, histopathologic examination, clinical follow-up examination, and radiologic examination in different combinations. None of these studies is perfect as a reference standard for confirming the diagnosis of infection. Miscategorization bias as a result of inadequate standard methods may have an effect on the estimation of the statistical parameters of a tested method, which may inflate or deflate its diagnostic ability. The mix of some standard methods in the studies, however, perhaps diminished this factor.

Although this meta-analysis showed good insight into using $^{99m}$Tc-UBI in the diagnosis of infection, especially in musculoskeletal infection, it should be mentioned that it has some limitations.

The major limitations are the relatively small sample size with different underlying problems. The meta-analysis is much larger than the largest eligible study and indicates the need to include more large-scale evidence. The second limitation is the application of significant variability in the reference standard methods in the eligible studies and the nonperformance of statistical parameters according to the type of reference standard used, due to the lack of provision of separate results based on the reference standard in the eligible investigations. Third, the dosages of $^{99m}$Tc, the time of scanning post-administration of UBI, the study designs, and the age groups varied throughout the studies, but it is uncertain how these factors might affect the results. Fourth, the interpretation of the $^{99m}$Tc–UBI scan was based on qualitative or semiquantitative methods with 2 or 3 readers so that some diagnostic biases are to be anticipated. Fifth, even though we searched for all eligible studies, the fact that there were some missing studies was inevitable.

On the basis of the current study, $^{99m}$Tc–UBI imaging appears to have distinct merits as a diagnostic method in the detection of infection, especially in the musculoskeletal system. However, it cannot yet fully substitute for the existing tests used for the diagnosis of infection, especially in diabetic patients.

## CONCLUSION

The study demonstrated that $^{99m}$TcUBI scintigraphy can be used to identify an infectious process with 93.7% accuracy in early views; however, further investigations are recommended.

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